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(54) Suppositories, injectable solutions

(57) A preparation e.g. suppository or injectable solution containing an absorption promoter selected from specific classes of water-soluble compounds having chelating activity e.g. EDTA, preferably in the presence of a salt e.g. NaCl at a concentration exhibiting higher osmotic pressure than isotonic sodium chloride solution, and a medicine is found to promote absorption of the medicine through a gastrointestinal organ such as colon and rectum, and through vagina.

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FIG. 1

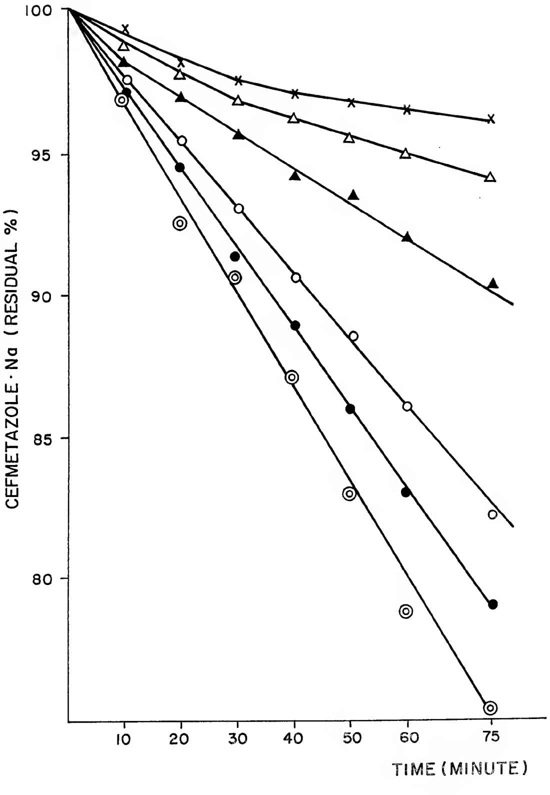

100
95
90
85
80
CEFMETAZOLE · Na (RESIDUAL %)
10
20
30
40
50
60
75
TIME (MINUTE)

FIG. 2

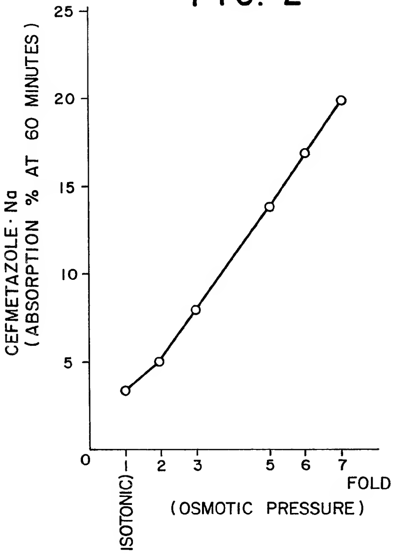

CEFMETAZOLE · Na
(ABSORPTION % AT 60 MINUTES)
25
20
15
10
5
0
(ISOTONIC) 1
2
3
5
6
7
FOLD
(OSMOTIC PRESSURE)

FIG. 3

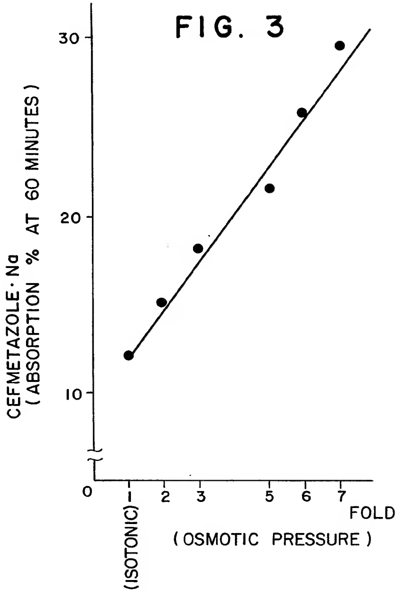

CEFMETAZOLE · Na
(ABSORPTION % AT 60 MINUTES)
30
20
10
0
(ISOTONIC) 1
2
3
5
6
7
FOLD
(OSMOTIC PRESSURE)

FIG. 4

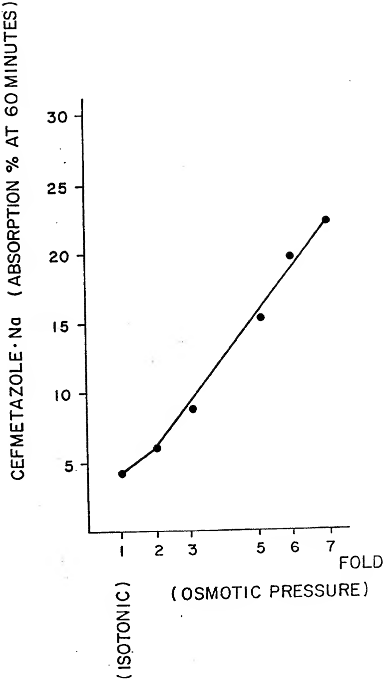

CEFMETAZOLE·Na (ABSORPTION % AT 60 MINUTES)
30
25
20
15
10
5
1
2
3
5
6
7
FOLD
(OSMOTIC PRESSURE)
(ISOTONIC)

FIG. 5

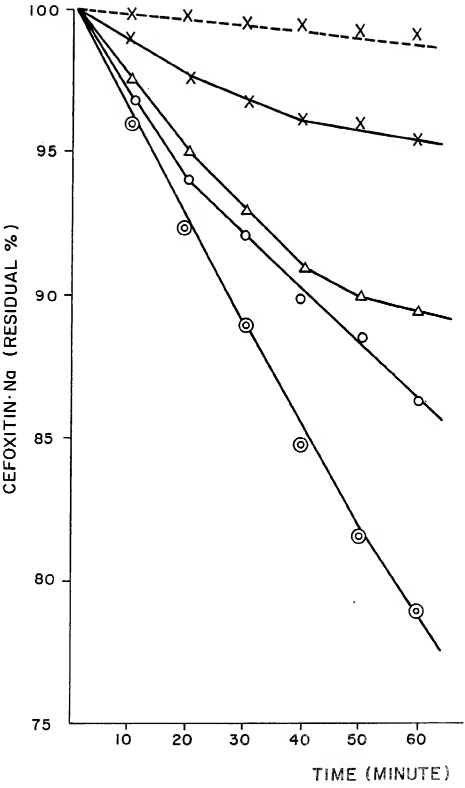

100
95
90
85
80
75
CEFOXITIN·Na (RESIDUAL %)
10
20
30
40
50
60
TIME (MINUTE)

FIG. 6

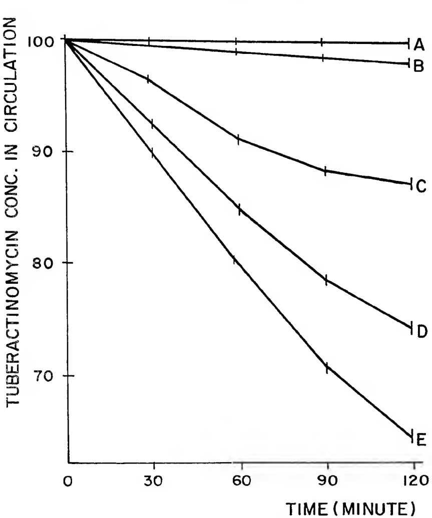

TUBERACTINOMYCIN CONC. IN CIRCULATION (%)
100
90
80
70
A
B
C
D
E
0
30
60
90
120
TIME (MINUTE)

FIG. 7

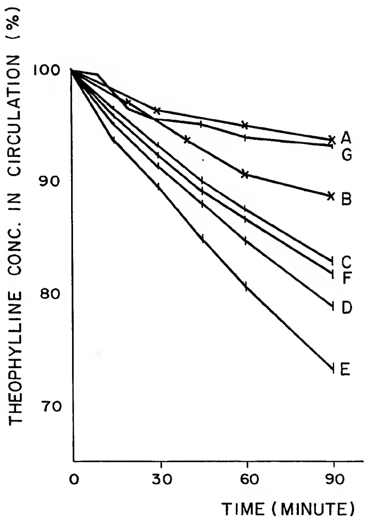

THEOPHYLLINE CONC. IN CIRCULATION (%)
100
90
80
70
A
G
B
C
F
D
E
0
30
60
90
TIME (MINUTE)

FIG. 8

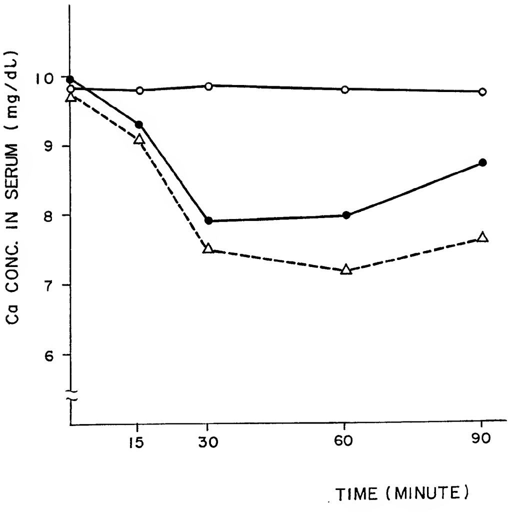


FIG. 9

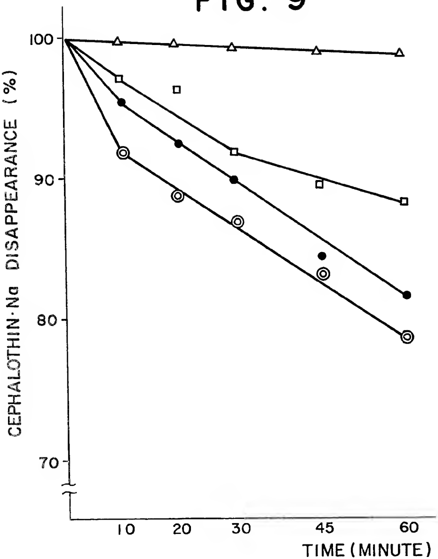
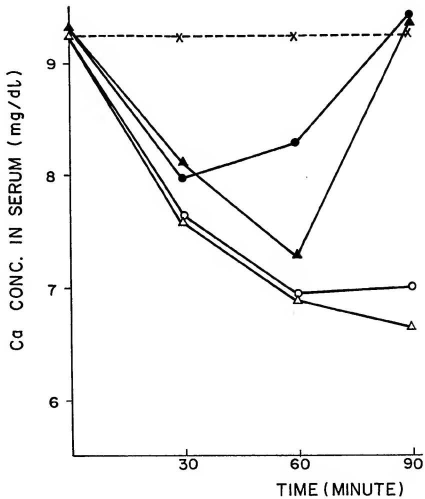

100
90
80
70
CEPHALOTHIN·Na DISAPPEARANCE (%)
10
20
30
45
60
TIME (MINUTE)

FIG. 10


9
8
7
6
Ca CONC. IN SERUM (mg/dL)
30
60
90
TIME (MINUTE)

SPECIFICATION

Preparation having excellent absorption property

This invention relates to a novel preparation having excellent absorption property which is intended for improvement of absorption of a medicine poor in absorption property through rectum or other digestive organs in a body by administration of such a medicine into rectum or others simulataneously with a water-soluble substance exhibiting higher osmotic pressure than isotonic sodium chloride solution and a water-soluble compound having chelating action. Further, it also pertains to a preparation having good adsorption property comprising a water-soluble macromolecular compound having chelating activity and a medicine, which can improve absorption property to a great extent of a medicine, which is itself poor in absorption property, and also maintain a high concentration thereof in blood for a long time.

Absorption of a medicine through a digestive organ, irrespective of whether it may be stomach, small intestine, large intestine, rectum or mouth, has heretofore been generally believed to proceed according to pH Partition theory (Modern Pharmaceutics, Marcel Dekker, INC., p. 31–49). Hence, a medicine readily dissociated in respective organs at absorption sites or a medicine having poor lipophilicity tends to be poorly absorbed. Such difficulty absorptive medincines are administered as injections under the present circumstances. For improvement of absorption property of a medicine, there have been made various investigations such as Prodrug, Sofdrug, utilization of ion pairs or complex formation. But any of these proposals is effective specifically for individual medicines, and no universally applicable method is known in the art ("Pharmaceutics" written by Nogami).

The present inventors have made various investigations and consequently found that in the mechanism of membrane absorption through digestive organs or others, which is believed to proceed according the pH Partition theory as mentioned above, a compound having a chelating action capable of bonding at least calcium ions or magnesium ions causes a change in membrane permeability, whereby membrane absorption of a medicine can be improved to promote successfully absorption thereof. It has also been found that a water-soluble macromolecular compound having a chelating action capable of bonding at least calcium ions or magnesium ions is also useful as a compound having such an absorption promoting action. Further, it has also been found that membrane absorption can be markedly improved by addition of a water-soluble substance at a concentration exhibiting higher osmotic pressure than isotonic sodium chloride solution to make the preparation under condition of higher tonicity than the osmotic pressure of a body fluid. In addition to these findings, it has further been found that a preparation obtained by use of vehicle, additives selected as desired and an objective medicine, for example, a suppository to be inserted into rectum or vagina is a good suppository which can excellently be absorbed through membranes and maintain a high concentration of the medicine in blood for a long time. The medicines to be used in the present invention are very broad. In particular, so called water-soluble medicines having good solubility in water, for example, those with partition coefficients of 50 or less in chloroform/water or mdicines readily dissociated into ions, are useful. Further, medicines applicable only as injections in the prior art are also found to be made excellently absorbable easily as preparations such as suppositories, Even a medicine with a high molecular weight such as polypeptide hormones is also found as the result of this invention to be made efficiently absorbable in the form of a preparation such as suppository.

The present invention has been accomplished based on the above findings, and the object of the present invention is to provide a good preparation in which a medicine can be improved to have a markedly enhanced absorption property.

In the accompanying drawings,

Figure 1 shows disappearance curves for various osmotic pressures of Cefmetazole when using Cefmetazole·Na as medicine, in which the percentages of Cefmetazole disappeared by absorption are plotted versus measurement time;

Figures 2, 3 and 4 variation curves of percentages of disappearance of Cefmetazole·Na versus osmotic pressure, respectively;

Figure 5 a disappearance curve of Cefoxitin·Na versus osmotic pressure;

Figure 6 disappearance curves of respective samples (A, B, C, D and E) in Example 4;

Figure 7 disappearance curves of respective samples (A, B, C, D, E, F, and G) in Example 7;

Figure 8 a curve of calcium concentration in serum when using Elcitonin as medicine;

Figure 9 a disappearance curve of Cephalothin·Na versus osmotic pressure; and

Figure 10 a curve of calcium concentration in serum when using Elcitonin as medicine.

According to the present invention, a preparation is provided which comprises a water-soluble substance at a concentration exhibiting an osmotic pressure high than isotonic sodium chloride solution, a water-soluble compound having chelating acitivity and a medicine.

According to the present invention, there is also provided a preparation, which comprises a

water-soluble macromolecular compound having chelating activity and a medicine.

To speak first of a water-soluble substance to be used in the present invention at a concentration exhibiting higher osmotic pressure than isotonic sodium chloride solution, it may preferably be one which is harmless as a whole and can exhibit high osmotic pressure with an amount as small as possible.

As such a water-soluble substance, there may be included water-soluble salts and water-soluble sugars.

Particularly among water-soluble salts, sodium chloride is preferred since it is safe and readily controllable of its osmotic pressure, and further soluble in water rapidly at a high dissolving rate. Further, mannitol or glucose is preferred among water-soluble sugars. Generally speaking, water-soluble salts may include, for example, halides, sulfates, phosphates or carbonates of alkali metals such as sodium, potassium or lithium, more specifically the aforesaid sodium chloride, sodium sulfate, disodium hydrogen phosphate, sodium dihydrogen phosphate, sodium phosphate, sodium hydrogen carbonate, sodium carbonate, potassium chloride, potassium sulfate, potassium hydrogen phosphate, potassium carbonate, lithium chloride, etc. These salts may be adjusted to concentrations exhibiting higher tonicity than osmotic pressure of isotonic sodium chloride solution depending on the osmotic characteristic thereof. For example, in case of sodium chloride, it may generally be adjusted to a concentration of 1 W/W % or higher for whole content. The upper limit of the concentration is not particularly limited, but preferably the concentration is about 2 to 30 W/W %. As preferable water-soluble sugars, there may be employed monosaccharides or disaccharides frequently used for adjustment of osmotic pressure in pharmaceutical technology, including, for example, glucose, mannitol, sorbitol, xylitol, lactose, maltose and sucrose. Such a sugar may be used at a concentration with higher tonicity than isotonic sodium chloride solution, which is generally 0.25 M or higher. These water-soluble substances may be used in combination of two or more kinds for adjustment of osmotic pressure, which is preferably 1.5 to 6-fold of the osmotic pressure exhibited by isotonic sodium chloride solution.

In connection with osmotic pressure, description is herein made by comparison with isotonic sodium chloride solution, but such a description with the use of isotonic sodium chloride solution as Control is merely exemplary for comparison between osmotic pressures, and therefore may also be possible with the use of body fluids or other solutions of salts with tonicity equal to such isotonic sodium chloride solution.

Referring now to the compounds having chelating action to be used as absorption promoters in this invention, they were investigated by adding to, for example, isotonic preparations for rectal application containing a medicine for examination of increase or decrease of membrane absorption of the medicine to accomplish the present invention. The mechanism of promotion effect has not so far been clarified, but it seems likely that membrane absorption mechanism may be changed through the chelating action and affinity to membrane possessed by these absorption promoters on the structures of cell membranes or the spaces between the epithelial cells thereby to promote absorption. Although the mechanism of action of the absorption promoter for increase of membrane absorption through rectum or other organs may be speculated as mentioned above, such a mechanism action is still no more than mere estimation and it is only sufficient to employ a compound having chelating action capable of bonding to at least calcium ions or magnesium ions. More specifically, as the chelating ligands for effective chelating action, there may be mentioned, for example, acid groups such as carboxylic acid group, sulfonic acid group, phosphoric acid group, phenolic hydroxyl group, etc., hydroxyl group, imino group, carbonyl group, amino group, etc. Further, as the compounds having chelating action with these chelating ligands, there may be included organic compounds having at least one acid groups, as exemplified by organic compounds having acid groups such as caboxylic acid groups, thiocarboxylic acid groups, sulfonic acid groups or phosphoric acid groups, organic acid compounds having acid groups having phenolic hydroxyl groups or organic compounds having at least 2 carbonyl groups. As the organic compounds having at least carboxylic acid group, sulfonic acid group or phosphoric acid group, there may be included various compounds having carboxylic acid groups, sulfonic acid groups or phosphoric acid groups such as monocarboxylic-, sulfonic– phosphoric-compounds or keto-carboxylic-, sulfonic-, phosphoric-compounds having carbonyl groups, hydroxy- or amino-carboxylic-, imino-carboxylic-, sulfonic-, phosphoric-compounds having hydroxyl groups or amino groups and polyacid compounds having two or more carboxylic acid groups, sulfonic acid groups or phosphoric acid groups. These compounds may also be classified into respective groups of aliphatic compounds, alicyclic compounds, aromatic compounds and heterocyclic compounds. Further, keto-enol type tautomeric isomers may be classified either as compounds having carbonyl groups or as compounds having hydroxyl groups. Further, compounds having plural kinds of groups such as carboxyl group, hydroxyl group, amino group and imino group are not necessarily clearly selected for each grouping. To set forth examples of these groups, polyacid compounds may include oxalic acid, malonic acid, succinic acid, glutaric acid, maleic acid, glutaconic acid, adipic

acid, fumaric acid, aconitic acid, pimellic acid, sebacic acid, suberic acid, azelaic acid, acridinic acid, allylmalonic acid, mesaconic acid, brassylic acid, dodecanolic acid, methylmalonic acid, ethylmalonic acid, phthalic acid, terephthalic acid, homophthalic acid, phenylsuccinic acid, phenylmalonic acid, phenylenediacetic acid, 1,3-naphthalenedicarboxylic acid, iminodiacetic acid, β-alaninediacetic acid, hydrochelidonic acid, 1,2-cyclohexanedicarboxylic acid, anthranylinoacetic acid, oxanylic acid-o-carboxylic acid, tricarballylic acid, 1,3-diamino-propanetetraacetic acid, hydroxyethyliminodiacetic acid, ethylendiaminediacetic acid, ethylenediaminedipropionic acid, hydroxyethylethylenediaminetriacetic acid, ethylene-diaminetetraacetic acid, ethyleneglycol-bis(β-aminoethyl ether) N, N′-tetraacetic acid, trans-cyclohexanediamine-tetraacetic acid, diaminopropanoltetraacetic acid, diethylenetriaminepentaacetic acid, ethylenediamine-di-o-hydroxyphenylacetic acid, triethylenetetraminehexaacetic acid, nitrilotriacetic acid, nitrilotripropionic acid and the like. Examples of hydroxy-acid compounds or phenolic hydroxyl group-acid compounds are lactic acid, citric acid, isocitric acid, malic acid, glyceric acid, tartaric acid, oxyacetic acid, dihydroxylethylglycinepanthotenic acid, pantoic acid, mevalonic acid, iduronic acid, saccharic acid, phosphenolpyruvic acid, 2-phosphoglyceric acid, 3- phosphoglyceric acid, glycero-3-phosphoric acid, glucose-1,6-diphosphoric acid, fructose-1,6-diphosphoric acid, α-oxybutyric acid, β-oxybutyric acid, gluconic acid, α-oxyisobutyric acid, glucuronic acid, galacturonic acid, leusinic acid, oxyglutamic acid, diethooxalic acid, atrolactinic acid, phenyllactic acid, maphthylglycolic acid, phenylhydroacrylic acid, benzylic acid, mandelic acid, salicyclic acid, 2, 5-dihydroxybenzoic acid, 2,3-dihydroxybenzoic acid, 2,6-dihydroxybenzoic acid, tetra-oxyhexahydrobenzoic acid, shikimic acid, melilotic acid, hexahydrosalicyclic acid, o-, m-, p-phenolsulfonic acid, 1,2-hydroxybenzene-3,5-disulfonic acid, 1-naphthol-2-sulfonic acid, 1-naphthol-3,6-disulfonic acid, 4-amino-phenol-2-sulfonic acid, and the like. Exemplary carbonyl-acid compounds are glyoxalic acid, glyoxylylacetic acid, acetoacetic acid, oxaloacetic acid, α-ketobutyric acid, acetopyruvic acid, puruvic acid, α-ketoglutaric acid, β-ketoglutaric acid, α-ketomalonic acid, α-ketovaleric acid, β-ketovaleric acid, benzoylformic acid, benzoylglycolic acid, benzoylpropionic acid, benzoylbutyric acid, levulinic acid, β-ketocapric acid, phenylpyruvic acid, oxanylic acid, and the like. Typical examples of monoacid compounds are butyric acid, isovaleric acid, caproic acid, caprylic acid, capric acid, undecylic acid, lauric acid, myrystic acid, palmitic acid, stearic acid, eicosanic acid, arachidonic acid, linoleic acid, linolenic acid, phenylthioacetic acid, phenylpropionic acid, α-phenylbutyric acid, acetylsalicyclic acid, anisic acid, phenylphosphoric acid and the like. A compound containing phenolic hydroxyl groups may be, for example, salicylic acid as mentioned above. Amino-acid compounds may include amino acids such as quinaldic acid, kynurenic acid, glycine, alanine, proline, hydroxyproline, phenylalanine, phenylglycine, thyrosine, cystine, cysteic acid, ε-aminocaproic acid, aspartic acid, glutamine, glutamic acid, leusine, isoleusine, serine, valine, threonine, methionine, p-hydroxyphenylglycine, alginine, tryptophan, hystidine, lysine, γ-carboxyglutamic acid, kynurenine and the like. Further, as the organic compounds having at least two carbonyl groups, there may be preferably employed enamine derivatives between amino acids (e.g. glycine, lysine, leusine, serine, phenylalanine, glutamic acid, thyrosine, phenylglycine, p-hydroxyphenyl-glycine, proline, hydroxyproline) and diketo compounds (e.g. acetylacetone, propionylacetone, butyroylacetone, 3-phenylacetylacetone, methylacetoacetate, ethylacetoacetate, ethyldiacetoacetate, propylacetoacetate, methoxyethylaceto-acetate, ethoxyethylacetoacetate, diethyl ethoxymethylene-malonate, dibutyl ethoxymethylmalonate, etc.). In addition, the above diketo compounds *per se* can also be employed as absorption promoters. These absorption promoters are generally used in the form of alkali metal salts such as sodium salts or potassium salts, or ammonium salts, but they may also be esterified to the extent such that water solubility is not impaired. In some of absorption promoters, for example, polyacid compounds such as ethylenediamine-tetraacetic acid (EDTA) or ethyleneglycol-bis(β-aminoethyl ether)-N,N′-tetraacetic acid (EGTA), a part of the acid groups may be protected by esterification, etc, to be converted to derivatives. In particular, in case of EDTA, one of the carboxylic groups may be converted to ethylester to obtain a derivative having better effect of promoting absorption of a medicine.

Further, as water-soluble macromolecular compounds having chelating action capable of bonding to at least calcium ions or magnesium ions, any water-soluble macro-molecular having two or more chelating ligands may be used. Typical examples are water-soluble polysaccharide compounds, water-soluble cellulose derivatives, dextran derivatives, water-soluble starch derivatives, water-soluble synthetic polymers, water-soluble peptide compounds or water-soluble derivatives thereof having two or more chelating ligands. These compounds may also be esterified to the extent such that chelating activity is not lost. These compounds may contain at least two of one or more kinds of chelating ligands selected from carboxylic acid groups, sulfonic acid groups, phosphoric acid groups, phenolic hydroxyl groups, hydroxyl groups, imino groups, carbonyl groups and amino groups, and they may either natural, semi-synthetic or synthetic products. Examples of these natural, semi-synthetic or synthetic water-soluble macromolecular compounds having chelating activity are enumerated below, but the present invention is not limited thereto.

Water-soluble polysaccarides containing uronic acid	:	alginic acid, pectinic acid, chondroitin sulfate, hyaluronic acid, arabic acid,
Water-soluble cellulose related commpounds	:	carboxymethyl cellulose, carboxyethyl cellulose, carboxypropyl cellulose, cellulose acetate phthalate;
Water-soluble starch relates compounds	:	carboxymethyl starch, carboxyethyl starch;
Detran related compounds	:	carboxymethyl dextran, dextran sulfate;
Polypeptide compounds	:	polyglutamic acid, poly-γ-carboxyglutamic acid, polyaspartic acid, polylysine, polyalginine and copolymers of these amino acids;
Water-soluble synthetic polymer compounds	:	polyacrylic acid, polmethacrylic acid, methacrylic acid-acrylic acid copolymer, acrylamide-acrylic acid copolymer, polyphosphoric acid

Further, these compounds or water-soluble base polymers exhibiting no detectable chelating activity may be bound with a chelating agent of low molecular weight having chelating activity to be converted to water-soluble macro-molecular compounds having chelating activity as a whole.

In this case, the base polymer may be any one having water-solubility and may be exemplified by synthetic polymers such as polyvinyl alcohol, polyethylene oxide, etc. or various natural polymers. Preferably, a polymer harmless to living bodies is employed and such a polymer may have side chain functional groups for introduction of chelater such as hydroxyl groups, carboxyl groups, amino groups or imino groups.

The polymer have a molecular weight which is not particularly limited, so long as it is soluble in water or capable of forming hydrogels, but generally in the range of from 1000 to 1,000,000.

Typical examples of such a water-soluble base polymer are set forth below, to which the present invention is not limited.

Typical examples of water-soluble base polymers

Polysaccharides containing uronic acid	:	chondroitin sulfate, heparin, arabic acid, pectin, gum tragacanth, tragacanthic acid, pectinic acid;
Other polysaccharides	:	carrageenan, β-guican, galactomannan, konjakamannan, galactan, fucan, inulin, levan;
Cellulose relates compounds	:	hydroxyethyl cellulose, hydroxypropyl cellulose, cellulose, methyl cellulose, ethyl cellulose hydroxypropylmethyl cellulose, agarose;
Starch relates compounds	:	soluble starch, phosphoric acid starch, acetyl starch, hydroxyethyl starch, dextrin, amylose, amylopectin;
Dextran relates compounds	:	dextran, diethylaminoethyl dextran, aminoethyl dextran;
Polypeptides	:	gelatin, casein, albumin, globulin;
Synthetic polymers	:	polyethylene glycol, polyvinyl alcohol, polyethylene oxide, vinyl acetate-maleic acid copolymer, vinyl acetate-crotonic acid copolymer, vinyl acetate-acrylic acid copolymer, polyvinyl alcohol-maleic acid copolymer, polyacrylamide, polyvinylacetal diethylaminoacetate, 2-vinylacetal diethylaminoacetate, 2-methyl-5-vinylpyridine/mkethyl acrylate/methacrylic acid copolymer.

As chelating agent to be incorporated into these water-soluble base polymers, there may be used a compound capable of forming a chelate with calcium ions or magnesium ions which can be introduced into the polymer side chain and has still chelate forming acitivity after introduction.

There may be employed a chelating agent which has an atomic group capable of forming a ring containing ligands between central metallic ions, can be introduced into the polymer side chain and coordinated with two or more molecules per metal ion. More preferably, the chelating agent may be one containing three kinds of ligand or functional group, namely a ligand (I) containing a proton as chelate forming functional group to be substituted by said metal ion (e.g. hydroxyl group, carboxyl group, imino group, etc.), a ligand (II) capable of coordination bonding to the metal ion (e.g. carbonyl group, amino group, etc.) and a functional group (III) for bonding chelater to the polymer side chain through formation of bondings such as amide bonding, ester bonding or ether bonding by reaction with side bonding of the above polymer (e.g. amino group, carboxyl group, hydroxyl group, halogen, etc.) and having a structure such that the chelate forming ligands (I) and (II) are separated by a link having 1 to 2 carbon atoms or that (I) and (II) are seprated from (III), which is the link with a polymer, by an organic group having 1 to 10 carbon atoms such as an aliphatic group or an aromatic group.

Typical examples of such compounds are enumerated below, but the present invention is not limited thereto.

Aliphatic polycarboxylic acid compounds	: oxalic acid, malonic acid, succinic acid, maleic acid, fumaric acid, aconitic acid, pimellic acid, sebacic acid, allylmalonic acid, ethylmalonic acid;
Aliphatic oxycarboxylic acid compounds	: citric acid, malic acid, glyceric acid, tartaric acid, mevaloic acid, oxyglutaric acid;
Aliphatic keto-poly-carboxylic acid compounds	: oxaloacetic acid, α-keto-glutaric acid, β-ketoglutaric acid, α-ketomalonic acid,
Uronic acid compounds	: glucuronic acid, galaceturonic acid, mannuronic acid;
Amino acid compounds	: aspartic acid, glutamic acid, glycine, alanine, lysine, hystidine, alginine, cysteine, ε-aminocaproic acid, phenyl-alanine, phenylglycine, p-hydroxyphenylglycine, p-amino-phenylalanine, γ-carboxyglutamic acid
Aminopolycarboxylic acid compounds	: iminodiacetic acid, hydroxy-ethyliminodiacetic acid, ethylenediaminediacetic acid, ethylenediamietetraacetic acid, trans-cyclohexanediaminetetra-acetic acid, diethylenediamine-pentaacetic acid, β-alanine-diacetic acid, diaminopimellic acid;
Aromatic carboxylic acid compounds	: phthalic acid, terephthalic acid, homophthalic acid, phenylsuccinic acid, phenylmalonic acid, oxanylic acid-o-carboxylic acid, anithra-lininoacetic acid, 2,4-dihydroxy-benzoic acid, p-aminosalicylic acid, phthalylglutamic acid, kynurenine,
Aliphatic and aromatic sulfonic acid compounds	: 1,2-hydroxybenzene-3,5-disulfo-nic acid, 4-aminophenol-2-sulfonic acid, cysteic acid;
Phosphoric acid compounds	: 2-phosphoglyceric acid, glycero-3-phosphoric acid, glucose-1,6-diphosphoric acid, fructose-1,6-diphosphoric acid.

For incorporation of such a chelating agent into a water-soluble base polymer, the chelating agent and the incorporation method to be employed are suitably selected depening on the side chains of the water-soluble base polymer employed, and the bonding formed as the result of the reaction is also determined by their combination, as descibed in detail in Japanese Patent Publication No. 16979/1979 (USP 4024073).

The effect of promoting absorption of a medicine by the water-soluble macromolecular compound having chelating activity obtained according to the present invention was examined by use of, for example, an Elcitonin preparation containing the lysine-dextran T-150 prepared according to Example 1 disclosed in Japanese Patent Publication No. 16979/1979 (USP 4024073) by intrarectal injection in vivo into rats and measuring decrease in calcium

concentration in serum, whereby it was found that said preparation exhibited significant absorption promoting effect as compared with Control using no lysine-dextran T-150. These macromolecular adsorption are generally used in the formed alkali metal salts such as sodium salts or potassium salts, or ammonium salts.

The water soluble low molecular compound and the macromolecular compound having chelating action or the water-soluble polymer having incorporated a chelating agent in the present invention is used as a membrane absorption promoter. These absorption promoters may be employed in amounts of 0.05 W/W % or more, generally in the range of from 0.1 to 50 W/W %, preferably from 1.0 to 30 W/W %. As the vehicle to be employed for preparation of a suppository containing the above absorption promoter, a medicine and preferably a water-soluble salt to be added for increase of tonicity, there may suitably be selected one from oily vehicles and water-soluble vehicles conventionally used in preparation of suppositories or rectal injections, and a surfactant may also be added if desired. It is a matter of course, two or more promoters may be used together.

As these oily vehicles or water-soluble vehicles, there may conveniently be used those as described in "The Theory and Practice of Industrial Pharmacy", p. 245 to 269 (1976).

The medicine to be used in the present invention is not particularly limited, but there may be employed ordinary pharmaceuticals, particularly preferably so called water-soluble medicines which are excellently soluble in water, such as water-soluble medicines with a partition coefficient of 50 or less in chloroform/water or medicines readily dissociated to ions. For example, there may be included various medicines such as hypnotics, tranquilizers, antiepileptics, antipyretics, antalgics, antidepressants, muscle relaxants, antiinflammatory agents, antiallergic agents, immunosuppressants, antirheumatics, vasodilators, anthemorragics, antihypertensives, antibiotics, antibaceterial agents, urinary tract sterilizers, antitumor agents, vitamins, hormones and galenicals. More specifically, typical examples are penicillin type antibiotics such as ampicillin, hetacillin, amoxicillin, cyclocillin, cloxacillin, dicloxacillin, oxacillin, carindacillin, sulbenicillin, piperacillin, apalcillin, methicillin, etc. or combined drugs of ampicillin or amoxicillin with oxacillin, cloxacillin, floxacillin or dichloxacillin; cephalosporin type antibiotics such as cephalothine, cephazoline, cephaloridine, cephacetorile, cefoxitin, cefadroxil, cefatrizine, cephaloglycin, cephalexin, cephapirin, cehphaclor, ceftezol, cefuroxime, cefsulodin, cefmetazole, etc. and non-toxic salts thereof such as alkali metal salts (e.g. sodium salts or potassium salts), ammonium salts or benzylamine salts. In addition, there may also be mentioned tetracycline type antibiotics such as doxycycline, oxycycline, etc.; aminosaccharide type antibiotics such as kanamycin, sisomicin, amikacin, tobramycin, netromycin, gentamycin, etc.; peptide type antibiotics such as tuberactinomycin N, actinomycin, etc. or non-toxic salts thereof; further peptide hormones such as insulin, somatostatin, calcitonin, angio-tensin, kallikrein, secretin, gastrisin, parathyroid hormone, etc.; and other medicines such as barbital, theophylline, aspirin, mizoribine, bredinin, 5-fluorouracil, methotrexate, L-dopa, etc. The medicine may be employed in an amount, which may suitably be selected and designed. For example, in case of antibiotics such as β-lactam antibiotics, 20 to 500 mg activity, generally 100 to 300 mg activity, or in case of peptide hormones such as insulin, 1 to 500 units may be contained per gram of preparation. In general the medicine may preferably be used in finely divided forms with 1 to 50μ diameters or as an aqueous solution.

The step of forming preparations may be performed according to conventional methods for production of preparations in general such as rectal suppository, urethral suppository or vaginal suppository ointments of creams. For example, the absorption promoter selected, a water-soluble substance in an amount exhibiting higher osmotic pressure than isotonic sodium chloride solution and a medicine are added to a vehicle, optionally in combination with a surfactant, and these components are thoroughly mixed to provide preparations.

Further, in production of these preparation, there may also be added preservatives such as methyl- or propyl-p-oxybenzoate, colorants, aromas and stabilizers.

The present invention is further illustrated in detail by referring to the following Examples, by which the present invention is not limited at all but various medicines, hypertonicators and absorption promoters may be selected and combined in addition to those shown in Examples.

Example 1

Absorption effects under conditions with various tonicities were examined. Each sample solution was prepared by adding 0.1 W/W % Cefmetazole·Na as medicine together with sodium oxalate or sodium glyoxalate as absorption promoter to a phosphate buffer of pH 7.0 conditioned with soidum chloride to a tonicity which is varied from isotonic to twice hypertonic than isotonic(two-fold tonicity), three times hypertonic than isotonic(three-fold tonicity), 5 times hypertonic than isotonic(five-fold tonicity), 6 times higher than isotonic(six-fold tonicity) and 7 times hypertonic than isotonic(seven-fold tonicity).

The experiment was conducted in the following manner. Namely, Sprague Dawleg rats (male), weighing 200 to 300 g, were narcotized (after fast for 20 hours) with pentobarbital (50 mg/kg)

and thereafter subjected to hypoabdominal incision for a first cannulation at a position about 1.5 cm from anus and also another cannulation at a position 5 cm upper than said first cannulation. Subsequently, rectum was internally washed with about 50 ml of isotonic sodium chloride solution kept at 38°C, and samples each of 10 ml were circulated through rectum for 5 minutes (2 ml/minute) to make the concentration in the system constant. Then, 5 ml of each sample was circulated at a flow rate of 2 ml/minute, and samples each of 0.05 ml were collected at intervals of 10 minutes from 0 minute. Each sample was diluted to 5 ml with distilled water and the quantity of medicine disappeared by absorption was determined by UN-spectro photometer.

As the result, the disappearance curve of Cefmetazole·Na under the condition of 0.1 W/W % sodium oxalate was obtained as shown in Fig. 1, in which x–x shows the result under the isotonic condition, △–△ under two-fold tonicity, ▲–▲ under three-fold tonicity, ○–○ under five-fold tonicity, ●–● under six-fold tonicity and ◎–◎ under seven-fold tonicity.

Fig. 2 also shows the absorption curve of Cefmetazola·Na under the above condition of 0.1 W/W % sodium oxalate at respective osmotic pressures.

Fig. 3 shows the absorption curve of Cefmetazole·Na under the conditions of 0.2 W/W % sodium oxalate at respective osmotic pressures.

Further, Fig. 4 shows the absorption curve of Cefmetazole·Na under the condition of 0.5 W/W % sodium glyoxalate at respective osmotic pressures.

Example 2

Using 0.1 W/W % Cefoxitin·Na as medicine and 0.5 W/W % of sodium glyoxalate as absorption promoter under respective osmotic pressure conditions (namely two-fold, four-fold and six-fold tonicities with the use of sodium chloride) and following otherwise the same procedure as in Exampe 1, quantities of Cefoxitin disappeared by absorption were determined by UV-spectro photometer similarly as in Example 1.

The results are shown in Fig. 5, in which x---x is the disappearance curve by absorption only of Cefoxitin under isotonic condition without use of sodium glyoxalate, x–x the disappearance curve of Cefoxitin with the use of sodium glyoxalate under isotonic condition, △–△ that under two-fold tonic condition, o–o that under four-fold tonic condition, and ◎–◎ that under six-fold tonic condition, respectively.

Example 3

Quantities of 0.5 W/W % Cefmetazole·Na disappeared by absorption under isotonic and three-fold tonic conditions were determined, respectively, using sodium malate, sodium pyruvate, sodium phosphenolpyruvate, sodium β-hydroxybutyrate, sodium β-hydroxy glutarate, and sodium 2-phospho-D-glycerate. The results are shown in Table 1.

Table 1 (values after 60 minutes)

	Osotonic condition	Three-fold tonic condition
Sodium malate	4.9%	10.2%
Sodium pyruvate	5.2%	10.9%
Sodium phosphenolpyruvate	7.3%	16.6%
Sodium β-oxybutyrate	6.6%	14.0%
Sodium β-oxyglutarate	7.8%	16.5%
Sodium 2-phospho-D-glycerate	5.4%	13.8%

When no absorption promoter was employed, the quantity of 0.1 W/W % Cefmetazole·Na disappeared by absorption under isotonic condition was substantially negligible.

Example 4

Using 0.01 % solution of Tuberactinomycin, rectum circulation experiments were conducted in the same manner as in Example 1, and the Tuberactinomycin concentrations in the Perfusates were determined by measurement of antimicrobial activities (according to Japanese antimicrobial standards) with lapse of time. As the result, absorptions through rectum were fround to be increased by the presence of EDTA·2Na and sodium chloride, as shown in Fig. 6.

Sample A (Control): 0.01% Tuberactinomycin
0.9% sodium chloride
Sample B (Control): 0.01% Tuberactinomycin
5% sodium chloride
Sample C (Present invention): 0.01% Tuberactinomycin
5% sodium chloride

Sample D (Present invention): 0.05% EDTA disodium salt
0.01% Tuberacetinomycin
5% sodium chloride
0.1% EDTA disodium salt

Sample E (Present invention): 0.01% Tuberacetinomycin
5% sodium chloride
1% EDTA disodium salt

(Each sample was dissolved in 0.1 M Tris-HCl buffer and adjusted to pH 7.5.)

Example 5

Using 1% solution of Tuberacetinomycia (in 0.1 M Tris-HCl buffer, pH 7.5) as Control, an injection agent was prepared by adding 5% sodium chloride and 1.0% EDTA disodium salt to said solution. Each 0.5 ml of these samples was injected into rat through anus and the concentration of Tuberactinomycin in blood was measured to find that it appeared in blood at concentrations shown below.

	Concentration in blood (γ/ml)					
	10 min.	20 min.	30 min.	45 min.	60 min.	90 min.
Control:	lower than measureable limit of anti-microbial activity					
Present invention:	5γ	10γ	11γ	8γ	7γ	2γ

Example 6

Using 2% solution of Cephalotin·Na (in 0.1 M Tris-HCl buffer, pH 8.0) as Control, and injection agent was prepared by adding 6% sodium chloride and 1.0% disodium EDTA mono-ethylate to said solution. Each 0.5 ml of these samples was injected into rat through anus, and concentrations of Cephalothin in blood were determined by measurement of antimicrobial activities (according to Japanese anti-microbial standards) to find the concentrations in blood were significantly increased.

	Concentration in blood (γ/ml)					
	10 min.	20 min.	30 min.	45 min.	60 min.	90 min.
Control:	−	±	<1γ	<1γ	−	−
Present invention:	8γ	12γ	14γ	5γ	3γ	−

Example 7

Using 0.04% solution of Theophylline (in 0.1 M Tris-HCl buffer, pH 8.0), concentrations of circulated fluids were measured by UV absorption (λ_{max} = 270 nm) with lapse of time similarly as in Example 1, whereby absorption by rectum was found to be increased by the presence of EDTA·2Na and sodium chloride as shown in Fig. 7.

A (Control): 0.04% Theophylline, 0.9% sodium chloride
B (Control): 0.04% Theophylline, 0.1% EDTA disodium salt, 0.8% sodium chloride,
C (Present invention): 0.04% Theophylline, 0.1% EDTA disodium salt, 2% sodium chloride
D (Present invention): 0.04% Theophylline, 0.1% EDTA disodium salt, 4% sodium chloridie
E (Present invention): 0.04% Theophylline, 0.1% EDTA disodium salt, 8% sodium chloride
F (Present invention): 0.04% Theophylline, 1.0% EDTA disodium salt, 4% sodium chloride
G (Present invention): 0.04% Theophylline, 4.0% EDTA disodium salt, 4% sodium chloride

(Every sample was dissolved in 0.1 M Tris-HCl buffer and pH was adjusted all to 8.0.)

Example 8

An intrarectal injection preparation was obtained by adding calcitonin (CT: 625 mu/ml)based one the total amount; 25 ng/0.2 ml), sodium oxalate (0.2 W/W % based on the total amount) and glucose (isotonic; 0.25 M, three-fold tonic, 0.75 M, six-fold tonic; 1.5 M) to a base of carboxyvinyl polymer (CVP: Wako Gel 105, produced by Wako Junyaku Co., Ltd.) and 0.2 ml of this preparation was injected into rats (SD rats, four weeks of age). Calcium concentration after one hour was measured, and the relative effects were evaluated as compared with calcium concentration by CVP and CT which was set at standard value of 1. The results are shown in Table 2.

Table 2

Medicine	Isontonic	3-fold tonic	6-fold tonic
CT	1	1.05	1.67
CT + sodium oxalate	5.4	6.9	10.9

Example 9

Suppositories having the following compositions were inserted through anus into six male beagledogs, weighing 9.5 to 10.5 kg, and concentrations in blood were measured 15 minutes, 30 minutes, 60 minutes, 120 minutes and 180 minutes after administration to obtain the results as shown in Table 3.

Control: Suppository comprising 100 mg activity of Tuberactinomycin N·sulfate puverized to 50 microns or less and 400 mg of cacao butter

Present invention: Suppository comprising 100 mg activity of Tuberacetinomycin N·sulfate, 50 mg of sodium chloride, 10 mg of EDTA·2Na and 180 mg of cacao butter

Table 3

Beagledog No.		Concentration in blood (γ/ml)				
		15 min.	30 min.	60 min.	120 min.	180 min.
Control	1	—	0.8	0	—	—
	2	1.0	2.3	1.3	—	—
	3	—	1.5	—	—	—
	4	—	0.9	0.7	—	—
	5	—	—	—	—	—
	6	—	—	—	—	—
Present invention	1	3.9	12.0	7.6	4.2	2.2
	2	9.7	11.7	5.4	3.5	2.7
	3	9.2	10.0	8.1	4.8	3.0
	4	5.6	7.7	7.4	3.2	1.9
	5	10.8	9.2	7.3	6.0	2.0
	6	6.9	11.4	9.3	7.7	4.4

Example 10

As the group of polycarboxylic acid compounds (aliphatic compounds, there were employed sodium oxalate, malonic acid, maleic acid, fumaric acid, adipic acid, glutaric acid, pimellic acid, EDTA·2Na, trans-cyclohexane-diaminetetraacetic acid (CyDTA), iminodiacetic acid, nitrilotriacetic acid, ethylmalonic acid, trans-aconitic acid, diaminopropanoltetraacetic acid (DTPA-OH), each at a concentration of 0.1% W/V, and the quantities of Cephalothin disappeared by absorption were determined one hour after administration of 0.1% W/V Cephalothin·Na under isotonic (X 1), two-fold tonic (X 2) and four-fold tonic conditions (X 4), respectively. The experiments were conducted similarly as in Example 1. That is, Wistar-strain male rats, weighing 250 to 300 g, were narcotized with pentobarbital (50 mg/kg) and thereafter subjected to hypoabdominal incision for a first cannulation at a position about 1.5 cm from anus and also another cannulation at a position 5 cm upper than said first cannulation. Subsequently, rectum was internally washed with about 20 ml of isotonic sodium chloride solution kept at 38°C, and each

sample was circulated at a flow rate of 2 ml/minute for 5 minutes to make the concentration in the system constant. Then, 6 ml of each sample was circulated at a flow rate of 2 ml/minute, and samples each of 0.05 ml were collected at intervals of 10 minutes. Each sample was diluted and the quantity of Cephalothin diappeared was determined by UV-spectro photometer or high-speed liquid chromatography.

The results of Cephalothin disappeared when collecting respective samples after one hour are shown below in Table 4.

Table 4

Group of polycarboxylic acids (aliphatic compounds)	Osmotic pressure X 1	X 2	X 4
No additon	1.2%	1.6%	3.1%
Sodium oxalate	6.6%	11.1%	18.3%
Malonic acid	4.5%	—	13.0%
Succinic acid	8.2%	13.1%	24.0%
Maleic acid	6.3%	10.6%	18.3%
Fumaric acid	5.5%	—	17.3%
Adipic acid	7.5%	11.2%	20.0%
Glutaric acid	5.7%	9.3%	15.2%
Pimellic acid	5.1%	7.8%	15.0%
EDTA·2NA	9.4%	17.1%	31.2%
CyDTA	8.1%	15.0%	32.3%
Iminodiacetic acid	7.1%	14.2%	17.0%
Nitrilotriacetic acid	4.4%	—	10.4%
DTPA-OH	7.5%	13.7%	21.6%
Trans-aconitic acid	10.5%	18.6%	27.8%
Ethylmalonic acid	12.3%	24.2%	36.9%

Example 11

As the group of aliphatic keto-carboxylic acid compounds, there were employed sodium glyoxalate, sodium pyruvate, sodium ketomalonate, sodium α-ketoglutarate, sodium oxaloacetate, α-ketobutyric acid, α-ketovaleric acid and levulinic acid each at a conclentration of 0.1 W/V % and the quantities of Cephalothin disappeared by absorption were determined one hour after administration of 0.1 W/V % Cephalothin·Na under isotonic (X 1), two-fold tonic (X2) and four-fold tonic conditions, respectively. The results are shown in Table 5. (The experimental method was the same as in Example 10, and units in Table are percents.)

Table 5

Group of aliphatic keto-carboxylic acids	Osmotic pressure X 1	X 2	X 4
Sodium glyoxalate	4.9	—	13.1
Sodium pyruvate	7.0	11.6	23.1
Sodium ketomalonate	8.4	12.7	19.6
α-ketoglutaric acid	7.1	—	25.6
Sodium oxaloacetate	13.8	17.5	22.2
α-ketobutyric acid	11.2	18.3	30.9
α-ketovaleric acid	9.8	14.7	23.2
Levulinic acid	11.9	21.1	34.3
No addition	1.2	1.6	3.1

Example 12

Using citric acid, malic acid, lactic acid, glucuronic acid and galacturonic acid as the group of aliphatic hydroxy-carboxylic acid compounds each at a concentration of 0.1 W/V %, quantities of Cephalothin disappeared by absorption were determined one hour after administration of 0.1 W/V % Cephalothin·Na under isotonic (X 1), two-fold tonic (X 2) and four-fold tonic (X 4) conditions, respectively. The results are shown in Table 6. (The experiment method was the same as in Example 10, and units in the Table are percents.)

Table 6

Group of aliphatic hydroxy-carboxylic acid compounds	Osmotic pressure X 1	X 2	X 4
Citric acid	4.5	—	11.3
Malic acid	7.2	12.3	18.8
Lactic acid	4.3	—	13.5
Glucuronic acid	5.5	11.1	16.4
Galacturonic acid	5.8	10.5	16.1
No addition	1.2	1.6	3.1

Example 13

Using as the group of aromatic carboxylic acids, sodium salicylate, sodium sulfosalicylate, sodium phthalate and 2,6-dihydroxybenzoic acid, each at a concentration of 0.5 W/V %, quantities of Cephalothin disappeared by absorption were determined one hour after administration of 0.1 W/V % Cephalothin·Na under isotonic (X 1), two-fold tonic (X 2) and 4-fold tonic (X 4) conditions, respectively. The results are shown in Table 7. (The experiment method was the same as in Example 10, and the units in the Table are percents.)

Table 7

Group of aromatic carboxylic acid compounds	Osmotic pressure X 1	X 2	X 4
Sodium salicylate	8.9	16.5	29.8
Sodium sulfonsalicylate	10.4	—	19.7
Sodium phthalate	7.1	—	18.9
2,6-dihydroxybenzoic acid	9.5	15.3	22.9

Example 14

As the group of aromatic sulfonic acid compounds, 1,2-dihydroxybenzene-3,5-disulfonic acid (DHBDS) and 1-naphthol-3,6-disulfonic acid (NDS) were employed, each at a concentration of 0.1 W/V %, and the experiments were performed similarly as in Example 10. The results are shown in Table 8, wherein the units are percents.

Table 8

Group of aromatic sulfonic acid compounds	Osmotic pressure X 1	X 2	X 4
DHBDS	9.8	—	22.0
NDS	12.6	19.8	31.6

Example 15

Example 1 was repeated except that butyric acid, isovaleric acid, sodium caproate, sodium caprylate, sodium caprate and sodium laurate were employed as aliphatic carboxylic acid compounds, each at a concentration of 0.1 W/V %, to obtain the results as shown in Table 9. (The units in the Table are percents.)

Table 9

Fatty acids	Osmotic pressure X 1	X 2	X 4
Butyric acid	9.9	17.1	21.0
Isovaleric acid	7.7	—	14.4
Sodium caproate	10.4	14.7	17.2
Sodium caprylate	5.8	—	13.0
Sodium caprate	5.2	—	8.6
Sodium laurate	3.9	—	6.5

Example 16

Example 10 repeated except that the aliphatic carboxylic compounds were replaced with ethylacetoacetate and 3-phenylacetyl acetone as diketo-compounds to obtain the results as shown in Table 10, wherein the units are percents.

Table 10

Group of diketo-compounds	Osmotic pressure X 1	X 2	X 4
Ethylacetoacetate	14.6	20.2	26.7
3-Phenylacetyl acetone	9.1	16.3	22.2

Example 17

Example 10 was repeated except that the aliphatic carboxylic acid compounds were replaced with the group of amino-carboxylic acid compounds and imino-carboxylic acid compounds of DL-glycine, DL-hydroxyproline (each at 0.5 W/V %), DL-phenylalanine, DL-phenylglycine, N-phenylglycine, DL-aspartic acid, DL-glutamic acid, α-methyl DL-glutamate, DL-cysteic acid, ε-aminocaproic acid, N-dimethylphenyl-alanine, γ-carboxyglutamic acid, glycyl-DL-aminobutyric acid, glycyl-DL-aspartic acid (each at 0.1 W/V %). The results are shown in Table 11, wherein the units are percents.

Table 11

Group of amino-carboxylic acid and iminocarboxylic acid compounds	Osmotic pressure X 1	X 2	X 4
DL-glycine	6.9	9.4	14.0
DL-hydroxyproline	5.5	—	12.9
DL-phenylalanine	6.6	—	15.6
DL-phenylglycine	11.5	19.8	29.3
N-phenylglycine	12.0	22.3	30.8
DL-aspartic acid	11.6	15.6	22.4
DL-glutamic acid	12.1	—	22.3
α-methyl DL-glutamate	11.9	—	21.4
DL-cysteic acid	5.3	9.0	14.6
ε-aminocaproic acid	7.1	11.8	17.0
N-dimethylphenylalanine	10.9	—	25.5
γ-carboxyglutamic acid	13.1	24.6	31.4
Glycyl-DL-aminobutyric acid	11.0	—	30.4
Glycyl-DL-aspartic acid	8.6	—	19.0

Example 18

Example 10 was repeated except that as other acid compounds glycero-3-phosphoric acid, fructose-1,6-diphosphoric acid and ethylenediaminetetrakis(methylenephosphonic acid) (EDTPO)

were used each at 0.1 W/V % in place of the aliphatic carboxylic acid compounds. The results are shown in Table 12, wherein the units are percents.

Table 12

Acid compounds	Osmotic pressure X 1	X 2	X 4
Glycero-3-phosphoric acid	4.0	—	11.5
Eructose-1,6-diphosphoric acid	4.1	7.5	13.3
EDTPO	7.6	—	20.0

Example 19

Cephlothin·Na (1 g activity) as medicine, α-keto-glutaric acid·Na (1 g) as absorption promoter and sodium chloride (500 mg) as hypertonicator were each pulverized and mixed together. A homogeneous dispersion was prepared by adding to the resulting mixture a base of Witepsol H-15 previously molten by fusion to a total amount of 10 g. The dispersion was intrarectally administered at a dose of 50 mg/kg to Wistar-strain rats (male, weighing 250 to 300 g, four per one group) and blood sampling was performed 15 minutes, 30 minutes, 60 minutes and 120 minutes after administration for measurement of Cephalothin concentration in serum (according to the bioassay using Bacillus subtilis ATCC 6633). As Controls, there were also obtained a preparation containing sodium chloride without use of the absorption promoter (Control 1) and a preparation containing the absorption promoter without use of sodium chloride (Control 2). Further, another prepration of this invention was also prepared by use of 1 g of α-ketobutyric acid in place of the above absorption promoter, following otherwise the same procedure as described above.

As the result, Cephalothin concentrations for respective preparations were found as listed in Table 13.

Table 13

Preparation	Concentration in blood (γ/ml) 15 min.	30 min.	60 min.	120 min.
Control 1 (sodium chloride)	0.2	0.5	—	—
Control 2 (α-ketoglutaric acid·Na)	2.1	5.3	1.2	0.3
Present invention (α-ketoglutaric acid·Na/ sodium chloride)	5.9	11.4	3.1	1.2
Present invention (α-ketobutyric acid/ sodium chloride)	7.9	13.0	4.5	1.4

Example 20

Tuberactinomycin N·sulfate (1 g activity) as medicine, D-phenylglycine as absorption promoter (1 g) and sodium chloride as hypertonicator (500 mg) were each pulverized and thoroughly mixed. To the resulting mixtures, there was added Witepsol H-15 previously molten by heating, followed gy homogeneous dispersion, to provide a suppository for intrarectal administration. Example 19 was also repeated except that L-aspartic acid (1 g) was used in place of D-phenylglycine to obtain a suppository for intrarectal administration.

As Control, a preparation with the same composition as the above preparation except for containing no absorption promoter was also prepared. Each of these preparations was administered to rats and concentrations in blood were measured in the same manner as in Example 19 to obtain the results as shown in Table 14.

Table 14

Preparation	Concentrations in blood (γ/ml) 15 min.	30 min.	60 min.	120 min.
Control (sodium chloride)	0.9	1.8	0.3	—
Present invention (D-phenylglycine/ sodium chloride)	13.1	10.7	3.5	1.3
Present invention (L-aspartic acid/ sodium chloride)	8.4	10.3	2.8	0.9

Example 21

Ten units of Elcitonin[Asu. (1.7) eel calcitonin] as medicine, pulverized EDTA·2Na (20 mg) as absorption promoter and pulverized sodium chloride as hypertonicator (50 mg) were dissolved in 5% gelatin solution to an amount of 1 g, which was then administered intrarectally to S.D. rats of four weeks of age each in an amount of 0.1 ml. Calcium concentrations in serum were measured 15 minites, 30 minutes, 60 minutes and 90 minutes after administration according to the atomic absorption method. The same experiment was repeated except that 20 mg of CyDTA was employed in place of EDTA·2Na. Further, as Control, a preparation was prepared without use of the absorption promoter, followed by similar procedure. The results are shown in Fig. 8, in which ●–● indicate calcium concentrations in serum in case of the preparation containing EDTA·2Na as absorption promoter of this invention, △–△ indicating calcium concentrations in serum in the case of the preparation containing CyDTA of this invention and further o–o indicating calcium concentration in serum in the case of the as Control containing no absorption promoter.

Example 22

To a 0.1 W/W % Cephalothin·Na solution, there was added 0.1 W/W % pectinic acid and further mannitol was added at various levels to prepare isotonic solution, two-fold tonic solution and four-fold tonic solution, respectively. As Control, an isotonic solution without use of pectinic acid was also prepared. Subsequently, these samples were administered to Wistar-strain rats similarly as in Example 10 and quantities of Cephalothin disappeared by absorption were measured.

The results are shown in Fig. 9, wherein △–△ indicates the disappearance curve of Cephalothin in case of Control using no pectinic acid, □–□ disappearance curve in case of isotonic solution using pectinic acid, ●–● that of two-fold tonic solution using pectinic acid and ⊙–⊙ that of four-fold tonic solution using pectinic acid.

As apparently seen from Fig. 9, use of pectinic acid improves remarkably absorption of Cehalothin and further improvement is brought about by using in combination pectinic acid under hypertonic conditions.

Example 23

In place of pectinic acid in the above Example 22, there were employed sodium alginate, sodium carboxymethyl cellulose, sodium polyacrylate, chondroitin sulfate, sodium polyaspartate and sodium polyglutamate each at a concentration of 0.1 W/W %, and each solution was adjusted with sodium chloride to various tonicities, namely isotonic (X 1), two-fold tonic (X 2) and four-fold tonic (X 4) solutions. As the result, the quantities of Cephalothin disappeared at the time of sampling 60 minutes after circulation were found as shown in Table 15.

Table 15

Absorption promoter	Osmotic pressure		
	X 1	X 2	X 4
Sodium alginate	6.3%	10.2%	22.4%
Sodium carboxymethyl cellulose	7.1%	10.2%	18.7%
Sodium polyacrylate	6.7%	—	14.6%
Chondroitin sulfate	4.0%	6.7%	11.5%
Sodium polyaspartate	8.4%	11.5%	20.4%
Sodium polyglutamate	7.9%	15.0%	33.6%
No addition	1.2%	1 .6%	3.1%

Example 24

Using absorption promoters, prepared as described hereinafter in Reference examples, of aspartic acid-carboxy-methyl cellulose, iminodiacetic acid-alginic acid, imino-diacetic acid-carboxymethyl starch, glycine-starch, glycine-polyacrylic acid, ethylenediaminetetraacetic acid-dextran and hydrochelidonic acid-albumin, various samples of preparations were obtained with adjustment of tonicity to isotonic (X 1), two-fold tonic (X 2) and four-fold tonic (X 4). For each sample, the quantity of Cephalothin disappeared was determined similarly as in Example 10. As the result, the quantities of Cephalothin disappeared at the time of sampling 60 minutes after circulation were found as shown in Table 16.

Table 16

Absorption promoter	Osmotic pressure		
	X 1	X 2	X 4
Aspartic acid-carboxymethyl cellulose	7.0%	10.4%	22.6%
Iminodiacetic acid-alginic acid	7.2%	10.5%	24.6%
Iminodiacetic acid-carboxy-methyl starch	5.2%	9.8%	18.8%
Glycine-starch	5.1%	8.8%	11.9%
Glycine-polyacrylic acid	6.9%	10.1%	17.0%
Ethylenediaminetetraacetic acid-dextran	5.8%	9.2%	16.7%
Hydrochelidonic acid-albumin	4.2%	—	9.5%

Example 25

Elcitonin[Asu^{1,7}-eel calcitonin] (100 units and 10 units), sodium alginate (50 mg) and sodium chloride (50 mg) were dissolved in 1 ml of distilled water. Each solution (0.1 ml) was administered intrarectally to SD-strain male rats (four weeks of age) and calcium concentrations in serum were measured 30 minutes, 60 minutes and 90 minutes after administration by atomic absorption method. As Control, there was used a solution containing no sodium alginate (adjusted to 100 units of Elcitonin). Further, similar test was conducted by use of 50 mg of pectinic acid in place of sodium alginate.

The results are shown in Fig. 10, wherein X——X indicates calcium concentrations in serum in case of Control, o–o those in case of a solution containing sodium alginate and sodium chloride adjusted to 100 units of Elcitonin, △–△ those in case of a solution containing pectinic acid and sodium chloride at 100 units of Elcitonin, ●–● those in case of a solution containing sodium alginate and sodium chloride at 10 units of Elcitonin, ▲–▲ those in case of a solution containing pectinic acid and sodium chloride at 10 units of Elcitonin, respectively.

Example 26

Using ampicillin·Na (20 g potency) as medicine, sodium oxalate as absorption promoter (0.5 g) and sodium chloride (4 g) as water-soluble solution for higher tonic conditions, which are each pulverized, a homogeneous dispersion was prepared by adding these components to a

base of 50 g of peanut oil, followed further by dilution with peanut oil to a total amount of 100 g. The preparation was then filled in aliquots each of 1 g in gelatin soft capsules.

Example 27
Tuberacetinomycin N sulfate (20 g), sodium chloride (3 g) as water-soluble substance for hypertonic conditions and sodium oxalate as absorption promoter (0.2 g), which were each pulverized, were added to an oily base of peanut oil to a total amount of 100 g to obtain rectal capsules.

Example 28
Cefazolin·Na (200 g activity), D-phenylglycine (50 g) and sodium chloride (50 g) were each pulverized and mixed together. To the resulting mixture, there was added Witepsol W-35 molten by heating to 1 kg, followed by homogeneous dispersion. The dispersion was then molded in a suppository containing to provide suppositories each of 1 g.

Example 29
Ampicillin·Na (250 g activity), D-phenylglycine (200 g) and sodium chloridie (50 g), each being pulverized, were mixed and the resulting mixture was mixed with Witepsol H-15 molten by heating to an amount of 1 kg, which was further homogeneously dispersed. The dispersion was molded in suppository container to provide suppositories each of 1 g.

Example 30
Finely pulverized ampicillin·$3H_2O$ (250 g activity), α-ketobutyric acid (100 g) and finely pulverized sodium chloride (50 g) were mixed together. The resulting mixture was mixed with Witepsol W-35 molten by heating to an amount of 1 kg, followed by homogeneous dispersion. Suppositories each of 1 g were molded in suppository containers.

Example 31
Finely pulverized Cephalothin·Na (250 g Potency), ethyl acetate (100 g) and finely divided sodium chloride (50 g) were mixed with sesame oil to an amount of 1 kg to form a homogeneous dispersion. The dispersion was filled in aliquots each of 2 g into plastic injection cylinders to obtain intrarectal injection preparations.

Example 32
Tuberactinomycin N sulfate (500 g Potency), oxaloactic acid (100 g) and sodium chloride (50 g) were each pulverized and mixed. The mixture was mixed and homogeneously dispersed with Witepsol H-5 molten by heating to an amount of 1 kg. The dispersion was molded in suppository containers to provide suppositories (each 2.5 g).

Example 33
One hundred thousand units of Elcitonin, 20 g of finely pulverized CyDTA and 50 g of finely pulverized sodium chloride were added to Witepsol H-15 molten by heating to an amount of 1 kg, and the resulting mixture was molded in aliquots each of 1 g in suppository containers to provide suppositories (1 g).

Example 34
One hundred thousand units of Elcitonin, 30 g of finely pulverized sodium phenylpyruvate and 250 g of finely pulverized mannitol were dispersed by dissolution in 0.1% carboxyvinyl polymer solution (Wako Gel, trade name, produced by Wako Junyaku Co., Ltd.) to an amount of 1 kg, which was then injected into plastic applicators in aliquots each of 1 g to provide intrarectal injection preparations.

Example 35
Gentamycin (200 g Potency), sodium caproate (50 g) and sodium chloride (50 g) were each finely pulverized and mixed together. The mixture was mixed with Witepsol W-35 molten by heating to an amount of 1 kg, and the resulting mixture was molded in suppository containers to provide 1 g suppositories.

Example 36
Amicacin sulfate (200 g Potency), γ-ketoglutamic acid (50 g) and sodium chloride (50 g) were each finely divided and mixed together, and Witepsol H-15 molten by mixing was added to the mixture to an amount of 1 kg. Further, the resulting mixture was molded in suppository containers to provide 1 g suppositories.

Example 37

Cephalothin·Na (200 g Potency), sodium alginate (50 g) and sodium chloride (50 g), each being pulverized, were mixed and the resulting mixture was dissolved in 2% gelatin solution to a volume of one liter, which was then filled into injection cylinders in aliquots each of 1 ml to provide intrarectal injection preparations.

Example 38

Gentamycin (100 g Potency), sodium pectinate (50 g) and mannitol (250 g), each being pulverized, were mixed and the mixture was homogeneously dispersed in 5% gelatin solution to a volume of one liter, which was then filled into injection cyclinders in aliquots each of 1 ml to provide intrarectal injection preparations.

Example 39

One thousand units of Elecitonin, 50 g of sodium pectinate and 250 g of mannitol were each pulverized and mixed together. The resulting mixture was dispersed homogeneously in 5% gelatin solution to a volume of one liter, which was then filled into injection cylinders in aliquots each of 1 ml to provide injection preparations for vaginal suppository.

Example 40

One thousand units of Elcitonin, 50 g of sodium pectinate and 250 g of mannitol were dispersed homogeneously in Witepsol H-15 molten by heating to an amount of 1 kg, which was then filled in suppository containers in aliquots each of 1 g to provide rectal suppositories.

Example 41

One thousand units of Elcitonin, 50 g of sodium alginate and 5 g of sodium chloride were dissolved in 100 ml of distilled water and the solution was added to Witepsol H-5 containing 1% Span 60 (kproduced by Kao-Atlas Co.) to an amount of 500 g, followed further by homogeneous emulsifying. The emulsion was filled in suppository containers in aliquots each of 1 g to provide rectal suppositories.

Example 42

Cefoxitin·Na (200 g Potency), sodium alginate (50 g) and sodium chloride (50 g) each being pulverized were mixed and dispersed in Witepsol H-5 molten by heating to an amount of 1 kg, which was then filled in suppository containers in aliquots each of 1 g to provide suppsitories.

Example 43

Example 42 was repeated except that Cephazolin·Na (200 g Potency) was employed in place of Cefoxitin·Na to obtain suppositories.

Reference example 1

Ten grams of commercially available carboxymethyl cellulose·Na were dissolved in 400 ml of 17.5% sodium hydroxide solution and subjected to mercerization at 3 to 5°C under nitrogen atmosphere. The product was diluted to 2 litres with deionized water and then adjusted to pH 11 with hydrochloric acid. Then, 100 ml of an aqueous solution containing 5 g of bromocyan was added to the solution and the reaction was carried out at room temperature for 5 minutes. After the reaction was over, pieces of ice were added to cool the mixture to lower than 5°C, whereupon an aqueous solution of pH 10 containing 150 mmol of aspartic acid and 1 mmol of ethylenediaminetetraacetic acid was added and the reaction was carried out at 5°C overnight. After the reaction, the reaction mixture was neutralized with 6N-hydrochloric acid, concentrated under reduced pressure, further adjusted to pH 10.5 with 5 N-sodium hydroxide solution to dissolve insolubles formed during concentration. Then, the mixture was dialyzed against water and further against 0.01 N hydrochloric acid, followed by lyophilization to obtain 8.5 g of aspartic acid-carboxy-methyl cellulose.

Reference example 2

Sodium alginate (1.5 g) was dissolved in 100 ml of distilled water, adjusted to pH 8.0 and 10 mmol of hydroxysuccinimide was added thereto, and the reaction was carried at 5°C for 60 minutes to obtain an activated ester. After the reaction, 10 mmol of aminodiacetic acid was added to effect the reaction. Then, the reaction mixture was charged to Sephadex G-200 and eluted with 10 mM phosphate buffer (pH 6.5). The eluted fractions were recovered and lyophilized to obtain 1.0 g of iminodiacetic acid-alignic acid.

Reference example 3

Reference example 2 was repeated except that 1.5 g of carboxymethyl starch·Na was employed in place of sodium alginate to obtain 0.8 g of iminodiacetic acid-carboxymethyl starch.

Reference example 4

Using a commercially available soluble starch, after activation similarly as in Reference example 1, it was reacted with glycine to obtain 7.6 g of glycine-starch.

Reference example 5

After a commercially available sodium polyacrylate was subjected to activated esterification similarly as in Reference example 2, the reaction product was allowed to react with glycine to obtain 8.2 g of glycine-polyacrylic acid.

Reference example 6

A mixture of ethylenediaminetetraacetic acid, acetic acid, anhydride and pyridine was subjected to the reaction at 65°C for 24 hours to obtain dihydride of ethylenediamine-tetraacetic acid. The product was then added into dimethylformamide and further dextran was added to carry out the reaction. Distilled water was added to the reaction mixture, and the ethylenediamine-dextran was obtained by filteration.

Reference example 7

After hydrochelidonic acid was converted to an active ester similarly as in Reference example 6, the ester was reacted with albumin to obtain hydrochelidonic acid-albumin.

CLAIMS

1. A preparation having excellent absorption property, comprising a water-soluble substance at a concentration exhibiting higher osmotic pressure than isotonic sodium chloride solution, a water-soluble compound having chelating activity and medicine.

2. A preparation according to claim 1 wherein the water-soluble compound having chelating activity is a water-soluble low molecular weight compound having one or more chelating ligand.

3. A preparation according to claim 1 wherein the water-soluble compound having chelating activity is a water-soluble macromolecular compound having two or more chelating ligands.

4. A preparation according to claim 2 wherein the chelating ligand is selected from carboxylic acid group, sulfonic acid group, phosphoric acid group, phenolic hydroxyl group, hydroxyl group, carbonyl group, amino group, imino group or combinations thereof.

5. A preparation according to claim 3 wherein the water-soluble macromolecular compound having two or more chelating ligands is selected from water-soluble polysaccharide compounds, water-soluble cellulose derivatives, water-soluble starch derivatives, dextran derivatives and water-soluble polypeptide compounds and water-soluble synthetic polymer compounds having two or more chelating ligands.

6. A preparation according to claim 3 wherein the water-soluble macromolecular compound is a compound having chelate functional groups incorporated into a water-soluble base polymer.

7. A preparation according to claim 2 wherein the water-soluble low molecular weight compound having chelating ligand is a polycarboxylic acid compound, a hydroxycarboxylic acid compound, a keto-carboxylic acid compound or a monocarboxylic acid compound.

8. A preparation according to claim 2 wherein the water-soluble low molecular weight compound is an aminocarboxylic acid compound, an iminocarboxylic acid compound, an amino-polycarboxylic acid compound, or an iminopolycarboxylic acid compound.

9. A prepration according to claim 2 wherein the water-soluble low molecular weight compound having chelating ligand is a sulfonic acid compound or a phosphoric acid compound.

10. A preparation according to claim 6 wherein the water-soluble base polymer is selected from water-soluble poly-saccharides, water-soluble cellulose derivatives, water-soluble starch derivatives, dextran derivatives, water-soluble polypeptides and water-soluble synthetic polymers.

11. A preparation accordin to claim 6 wherein the compound having chelate functional group has one or more bonding functional group and two or more chelating ligands.

12. A preparation according to claim 11 wherein the compound having chelate functional group is an aliphatic polycarboxylic acid, an aliphatic hydroxycarboxylic acid, a uronic acid, an amino acid, an aminopolycarboxylic acid, an aromatic carboxylic acid, an aliphatic sulfonic acid, an aromatic sulfonic acid, a phosphoglyceric acid, a glycerophosphoric acid or a phosphoric acid ester of a saccharide.

13. A preparation according to claim 2 wherein the water-soluble low molecular weight compound having chelating ligand is one selected from the group consisting of succinic acid, ethylmalonic acid, adipic acid, transe aconitic acid, pyruvic acid, α-ketoglutaric acid, levulinic acid, oxaloactic acid, acetoacetic acid, butyric acid, salicyclic acid, 2,6-dihydrobenzoic acid, phthalic acid, phenylpyruvic acid, phenylmalonic acid, citric acid, malic acid, DL-aspartic acid, DL-glutamic acid, DL-phenylglycine, N-phenyl-glycine, γ-carboxyglutamic acid, N-phenylglycine ethyl ester, glycyl-DL-aminobutyric acid, N-dimethylphenylalanine, ethylenediamineteraacetic

acid, trans-cyclohexanediamine-tetraacetic acid, diethyltriaminepentaacetic acid, ethylene-di aminetetrakis(methylphosphonic acid), 1-naphthol-3,6-sulfonic acid, chromotropic acid, 1,2-di hydroxybenzene-3,5-disulfonic acid ethyl acetoacetate, or their salts.

14. A preparation according to claim 3, wherein the water-soluble macromolecular compound having two or more chelating ligands is selected from the group consisting of alginic acid, pectinic acid polyacrylic acid, polyaspartic acid and polyglutamic acid, or their salts.

15. A preparation according to claim 1 wherein the water-soluble substance at a concentration exhibiting higher osmotic pressure than isotonic sodium chloride solution is 1 W/W % or more of a water-soluble salt.

16. A preparation according to claim 15, wherein the water-soluble salt is a water-soluble salt of an alkali metal.

17. A preparation according to claim 16 wherein the water-soluble salt of alkali metal is a halide, a sulfate, a phosphate or a carbonate of sodium, potassium or lithium.

18. A preparation according to claim 1 wherein the water-soluble substance at a concentration exhibiting higher osmotic pressure than isotonic sodium chloride solution is a 0.25 M or more of a water-soluble saccharide.

19. A preparation according to claim 18 wherein the water-soluble saccharide is sorbitol, glucose, mannitol, maltose, lactose or sucrose.

20. A preparation according to claim 1 wherein the principal ingredient medicine is a water-soluble medicine having good water-solubility.

21. A preparation according to claim 20 wherein the water-soluble medicine has a partition coefficient of 50 or less in chloroform/water.

22. A preparation having excellent absorption property, comprising a water-soluble macromolecular compound having chelating activity and a medicine.

23. A preparation according to claim 22 wherein the water-soluble compound having chelating activity is a watersoluble machromolecular compound having two or more chelating ligands.

24. A prepration according to claim 23 wherein the chelating ligand is selected from carboxylic acid group, sulfonic acid group, phosphoric acid group, phenolic hydroxyl group, hydroxyl group, carbonyl group, amino group, imino group or combinations thereof.

25. A prepration according to claim 23 wherein the water-soluble macromolecular compound having two or more chelating ligands is selected from water-soluble polysaccharide compounds, water-soluble cellulose derivatives, water-soluble starch derivatives, dextran derivatives and water-soluble polypeptide compounds and water-soluble synthetic polymer compounds having two or more chelating ligands.

26. A preparation according to claim 23 wherein the water-soluble macromolecular compound having two or more chelating ligands is a compound having chelate functional groups incorporated into a water-soluble base polymer.

27. A preparation according to claim 26 wherein the water-soluble base polymer is selected from water-soluble polysaccharides, water-soluble cellulose derivatives, water-soluble starch derivatives, dextran deriviatives, water-soluble polypeptides and water-soluble synthetic polymers.

28. A preparation according to claim 26 wherein the compound having chelate functional group to be incorporated into the water-soluble base polymer has one or more bonding functional group and two or more chelating ligands.

29. A preparation according to claim 28 wherein the compound having chelate functional group to be incorporated into the water-soluble base polymer is an aliphatic polycarboxylic acid, an aliphatic hydroxycarboxylic acid, a uronic acid, an amino acid, an aminopolycarboxylic acid, an aromatic carboxylic acid, an aliphatic sulfonic acid, an aromatic sulfonic acid, a phosphoglyceric acid, a glycerophosphoric acid or a phosphoric acid ester of a saccharide.

30. A preparation according to claim 23, wherein the water-soluble macromolecular compound having two or more chelating ligands is selected from the group consisting or alginic acid, pectinic acid polyacrylic acid, polyaspartic acid and polyglutamic acid, or their salts.

31. A preparation according to claim 22 wherein the medicine is a water-soluble medicine having good water-solubility.

32. A preparation according to claim 31 wherein the water-soluble medicine has a partition coefficient of 50 or less in chloroform/water.

33. A preparation according to claim 1 substantially as hereinbefore described with specific reference to the Examples.

34. A preparation according to claim 22 substantially as hereinbefore described with specific reference to the Examples.

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